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Prospective study of abdominal adiposity and gallstone disease in US men[1–3]

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ABSTRACT

Background: Obesity is an established risk factor for gallstones, but whether abdominal adiposity contributes independently to the risk, particularly in men, remains unclear.

Objective: The purpose of the study was to examine the associations of abdominal circumference and waist-to-hip ratio, as measures of abdominal adiposity, with the risk of symptomatic gallstone disease in men.

Design: We prospectively studied measures of abdominal obesity in relation to the incidence of symptomatic gallstone disease in a cohort of 29 847 men who were free of prior gallstone disease and who provided complete data on waist and hip circumferences. Data on weight, height, and waist and hip circumferences were collected in 1986 and in 1987 through self-administered questionnaires. As part of the Health Professionals Follow-Up Study, men reported newly diagnosed symptomatic gallstone disease on questionnaires mailed to them every 2 y.

Results: We documented 1117 new cases of symptomatic gallstone disease during 264 185 person-years of follow-up. After adjustment for body mass index and other known or suspected risk factors for gallstones, men with a height-adjusted waist circumference $\geq$ 102.6 cm (40.4 in) had a relative risk of 2.29 (95% CI: 1.69, 3.11; *P* for trend $<$ 0.001) compared with men with a height-adjusted waist circumference $<$ 86.4 cm (34 in). Men with a waist-to-hip ratio $\geq$ 0.99 had a multivariate relative risk of 1.78 (1.38, 2.28; *P* for trend $<$ 0.001) compared with men with a waist-to-hip ratio $<$ 0.89.

Conclusions: Our data suggest the presence of a significant association between abdominal adiposity and the incidence of symptomatic gallstone disease. As measures of abdominal adiposity, abdominal circumference and waist-to-hip ratio predict the risk of developing gallstones independently of body mass index. *Am J Clin Nutr* 2004;80:38–44.

KEY WORDS Abdominal adiposity, gallstones, men, epidemiology

INTRODUCTION

Gallstones develop in ≈10–25% of adults in the United States and account for >800 000 hospitalizations yearly (1, 2). In the United States, cholesterol stones account for ≈80% of the gallstones removed from patients (3, 4). Although obesity is an established risk factor for cholesterol gallstones in both sexes, the association of gallstone disease with obesity tends to be found less consistently in men than in women (5–8). Several studies that found a positive relation between body mass index (BMI; in kg/m^2) and gallstone disease in women failed to show such an association in men (9–12), which raises the possibility that men may be less liable to gallstone formation associated with obesity because they may have more lean body mass than women do (13). Abdominal or central obesity, which is a powerful contributor to metabolic abnormalities such as insulin resistance and low plasma HDL cholesterol (14–16), may play an important role in gallstone formation (3, 9, 11, 17). Limited data on regional fat distribution suggest that central obesity may be related to the risk of gallstones (18–21), but this is not well established. Some studies failed to find an association with fat distribution (8, 22–24), particularly in men, but these studies may have been underpowered. Whether regional obesity represents an independent risk factor for gallstone disease after total adiposity is taken into account is unclear. To address the significance of the associations between body fat distribution and the risk of gallstone disease in men, we prospectively examined indicators of abdominal adiposity in relation to the occurrence of symptomatic gallstone disease in a large cohort of US men.

SUBJECTS AND METHODS

Population for analysis

The Health Professionals Follow-Up Study began in 1986 as a prospective study. The cohort comprises 51 529 US male dentists (58%), veterinarians (20%), optometrists (7%), osteopathic physicians (4%), and podiatrists (3%) who were 40–75 y of age and returned a mailed questionnaire regarding anthropometric measures, diet, medications, and medical history at baseline. Ninety-six percent of the participants are white. Follow-up questionnaires were sent biennially to update information on exposures and a variety of newly diagnosed illnesses, including gallstone disease. Diet was assessed in 1986, 1990, and 1994. After repeated mailings, the follow-up rate in each 2-y follow-up cycle was >94%. Follow-up for deaths was done through the next of kin, post office notification, and the National Death Index (25). A brief supplementary questionnaire was sent in 1987 to obtain

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self-reported waist and hip circumferences. The response rate to this questionnaire (≈65%) was lower than that for the usual biennial mailings because fewer follow-up mailings were conducted for this off-year questionnaire. For this analysis, we excluded 2007 men who reported a cholecystectomy or gallstone diagnosis at baseline. We also excluded 1208 men who were diagnosed with cancer before 1986, 2151 men who did not provide valid information on the questionnaires, and 16 316 men who did not provide weight or height information or complete waist and hip circumference measurements; these exclusions left 29 847 men for follow-up. The protocol of the Health Professionals Follow-Up Study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Documentation of gallstone cases

The primary endpoint was newly diagnosed symptomatic gallstone disease. In 1986 and on each biennial follow-up questionnaire, participants were asked whether they had undergone surgical removal of the gallbladder or had been diagnosed as having gallstones by a physician. Participants were also asked whether the gallstone diagnosis had been confirmed by ultrasonographic or X-ray procedures and whether their gallstones were symptomatic. For verification of the self-reports of cholecystectomy and diagnosed but unremoved gallstones, a random sample of 441 medical records of participants who reported a cholecystectomy or gallstones were reviewed, and of these, the diagnosis was confirmed in all except for 5 participants (99%). Moreover, all except for one of the self-reported diagnostic procedures were confirmed by medical record review.

Anthropometric assessment

The men reported their current weight and height and their weight at 21 y of age on the 1986 baseline questionnaires. In 1987 we mailed a supplementary questionnaire to all cohort members to obtain information on additional variables, including circumference, that were not included on the 1986 baseline questionnaire. Each participant was instructed to measure his waist at the umbilicus and his hips at the largest circumference between the waist and the thighs while standing; the participants were also instructed to avoid wearing bulky clothing during these measurements (26). A tape measure and an illustration were provided in the mailing to help standardize the measurements.

We used BMI, which was calculated by dividing weight (in kg) by the square of height (in m), as a measure of total adiposity, waist-to-hip ratio to measure the relative distribution of fat, and waist circumference to estimate abdominal fat (27). In this cohort, waist circumference was positively correlated with height. Thus, to investigate the association of waist circumference with gallstone disease independently of height, we adjusted waist circumference for height by using residual analysis to remove extraneous variation (27). We first regressed waist circumference on height by using linear regression and then added the subject's residual to the average waist circumference for a man of average height to convert this measure back to the initial scale.

In 1987 the validity of self-reported waist and hip circumference measures was assessed in a random sample of 123 participants living in the greater Boston area. The average of 2 measurements that were made by different technicians and spaced 6 mo apart was compared with the self-reported current weight and waist and hip circumference values on the most recent questionnaire. The differences in mean circumference between the technician measures and the self-reported measures were 0.91 cm (0.36 in) for the waist and −1.98 cm (–0.78 in) for the hips. After adjustment for age and random within-person variability from daily or seasonal fluctuations in measurements, the Pearson correlations between the self-reported measures and the average of the technicians' 2 measurements were 0.97 for weight, 0.95 for waist circumference, 0.69 for waist-to-hip ratio, and 0.88 for hip circumference (26). The correlations were essentially unchanged within strata of age, smoking status, or BMI. Thus, the self-reported measures of waist and hip circumference and weight appeared to be reasonably valid. Information on potential confounding variables, including diet, physical activity, and smoking status, was obtained from the baseline 1986 questionnaire (28).

Statistical analysis

For each participant, follow-up time accrued from completion of the 1987 questionnaire and ended at the month of cholecystectomy, diagnosis of symptomatic gallstones, death, or the end of the study on 31 January 1998, whichever occurred first. Men with silent gallstones or those whose gallstone diagnosis was not based on ultrasonography or radiograph, as well as men with cancer, were excluded from subsequent follow-up periods. Thus, the eligible population at risk comprised only those men who remained free of gallstone disease and cancer at the beginning of each 2-y follow-up interval. Pearson correlations between the anthropometric variables were calculated. The waist-to-hip ratio and waist circumferences at study entry were divided into 6 categories, and BMI was divided into 8 categories, with approximately equal numbers of men in each category.

The incidence rates were calculated by dividing the number of events by person-years of follow-up. Relative risks were calculated as the incidence rate of symptomatic gallstone disease among men in each category of waist circumference and waist-to-hip ratio compared with the incidence rate among men in the lowest category of each index, with adjustment for age in 5-y categories. Age-adjusted relative risks were calculated by using the Mantel-Haenszel summary estimator (29). For multivariate analyses, the estimated relative risks for symptomatic gallstone disease were simultaneously adjusted for potential confounding variables by using a pooled logistic regression model with 2-y time increments (30). This method accounts for variations in time to the outcome event and is asymptotically equivalent to Cox regression with time-dependent covariates if the time intervals are short and the probability of an event is small for each interval (31). Tests for linear trends were computed by using continuous variables in pooled logistic regression models. In multivariate models, we simultaneously included the anthropometric index or indexes and potential confounders. Potential confounding variables included age, recent weight change, cigarette smoking, alcohol intake, caffeine intake, dietary fiber intake, physical activity, and total energy intake. Although reported diabetes mellitus was associated with obesity and gallstone disease, we did not control for it in the multivariate models because adjusting for risk factors in the causal pathway would have inappropriately attenuated the true relative risk of obesity (29). All relative risks are presented with 95% CIs, and all reported P values are two-sided. All analyses were performed with SAS release 6.12 (SAS Institute Inc, Cary, NC).

TABLE 1
Baseline characteristics according to height-adjusted waist circumference of US men who participated in the Health Professionals Follow-Up Study[1]

Characteristic	Height-adjusted waist circumference (cm) <86.4 ($n = 4889$)	86.4 to <90.2 ($n = 4840$)	90.2 to <93.7 ($n = 4987$)	93.7 to <97.3 ($n = 4943$)	97.3 to <102.6 ($n = 5057$)	≥102.6 ($n = 5131$)	P for trend
Age (y)	50.3 ± 9.0[2]	52.0 ± 9.2	53.8 ± 9.4	54.9 ± 9.5	55.7 ± 9.5	56.2 ± 9.4	<0.001
BMI in 1986 (kg/m^2)	22.0 ± 3.1	23.2 ± 3.4	24.1 ± 3.7	24.8 ± 4.0	25.9 ± 4.1	28.6 ± 5.4	<0.001
BMI at age 21 y (kg/m^2)	21.1 ± 4.2	21.5 ± 4.6	21.7 ± 5.0	21.9 ± 5.3	22.4 ± 5.3	23.5 ± 5.9	<0.001
Current smoker (%)	8.1	8.1	7.3	8.7	8.5	9.1	<0.001
Regular use of NSAIDs (%)	6.2	6.4	6.8	7.0	7.3	7.4	<0.001
Regular use of thiazide diuretics (%)	0.5	1.0	1.2	1.5	1.9	2.6	<0.001
Physical activity (METs/wk)	27.5 ± 28.7	23.7 ± 29.4	20.4 ± 23.6	18.6 ± 21.5	16.3 ± 20.2	12.9 ± 19.1	<0.001
Total energy intake (kcal/d)	2043 ± 611	2019 ± 614	1992 ± 602	1991 ± 605	2006 ± 616	2004 ± 633	0.004
Alcohol intake (g/d)	10.6 ± 14.1	11.3 ± 14.7	11.6 ± 15.3	12.1 ± 15.5	12.3 ± 16.3	11.9 ± 17.1	<0.001
Caffeine intake (mg/d)	211 ± 237	223 ± 234	229 ± 236	243 ± 250	250 ± 253	269 ± 265	<0.001
Dietary fiber intake (g/d)	22.2 ± 7.8	21.4 ± 7.0	21.2 ± 6.9	20.8 ± 6.6	20.6 ± 6.6	20.1 ± 6.5	<0.001

[1] NSAIDs, nonsteroidal antiinflammatory drugs; METs, metabolic equivalent tasks, defined as a multiple of metabolic equivalents of sitting at rest.
[2] $\bar{x}$ ± SD (all such values).

RESULTS

We documented 1117 cases of symptomatic gallstone disease during 264 185 person-years of follow-up, and in 600 of these cases, cholecystectomy was required. Mean values for anthropometric measurements and other potential risk factors according to 6 categories of height-adjusted waist circumference at baseline or of waist-to-hip ratio at baseline are shown in **Tables 1** and **2**, respectively. Men with a higher height-adjusted waist circumference and waist-to-hip ratio were more likely to be sedentary and current smokers, to eat less dietary fiber, and to consume more caffeine. The prevalence of the use of diuretics and nonsteroidal antiinflammatory drugs tended to be higher among the heaviest men. Height-adjusted waist circumference was more strongly associated with current BMI ($r = 0.80$) than was waist-to-hip ratio ($r = 0.35$) and was modestly correlated with BMI at 21 y of age ($r = 0.36$). Waist-to-hip ratio was not correlated with BMI at 21 y of age ($r = 0.08$).

Height-adjusted waist circumferences (**Table 3**) and waist-to-hip ratios (**Table 4**) were positively associated with age-adjusted risks of symptomatic gallstone disease. The men with a height-adjusted waist circumference ≥ 102.6 cm (40.4 in) had a relative risk of 2.66 (95% CI: 2.11, 3.35; P for trend < 0.001) compared with those with a height-adjusted waist circumference < 86.4 cm (34 in). Similarly, the men with a waist-to-hip ratio ≥ 0.99 had a relative risk of 2.26 (95% CI: 1.78, 2.86; P for trend < 0.001) compared with those with a waist-to-hip ratio <0.89.

Multivariate models were used to adjust simultaneously for regional and total adiposity measures as well as for other risk factors for gallstone disease (Tables 3 and 4). The men with a height-adjusted waist circumference ≥102.6 cm (40.4 in) had a relative risk of 2.29 (95% CI: 1.69, 3.11) compared with those with a height-adjusted waist circumference < 86.4 cm (34 in). As a continuous variable, each additional 2.54 cm (1 in) of height-adjusted waist circumference was associated with a relative risk

TABLE 2
Baseline characteristics according to waist-to-hip ratio of US men who participated in the Health Professionals Follow-Up Study[1]

Characteristic	Waist-to-hip ratio <0.89 ($n = 4751$)	0.89 to <0.92 ($n = 5793$)	0.92 to <0.94 ($n = 4588$)	0.94 to <0.96 ($n = 4616$)	0.96 to <0.99 ($n = 4701$)	≥0.99 ($n = 5398$)	P for trend
Age (y)	50.2 ± 8.8[2]	52.2 ± 9.2	53.5 ± 9.3	54.9 ± 9.6	55.6 ± 9.3	56.7 ± 9.6	<0.001
BMI in 1986 (kg/m^2)	23.4 ± 3.8	24.0 ± 4.1	24.4 ± 4.3	24.8 ± 4.5	25.5 ± 4.7	26.5 ± 5.0	<0.001
BMI at age 21 y (kg/m^2)	21.9 ± 4.6	21.9 ± 5.0	21.9 ± 5.1	21.9 ± 5.3	22.1 ± 5.3	22.3 ± 5.6	<0.001
Current smoker (%)	7.3	7.0	8.0	7.9	9.4	10.2	<0.001
Regular use of NSAIDs (%)	6.1	6.9	6.3	6.5	6.7	7.6	<0.001
Regular use of thiazide diuretics (%)	0.7	1.1	1.2	1.5	1.7	2.4	<0.001
Physical activity (METs/wk)	26.4 ± 30.4	22.6 ± 25.9	20.3 ± 25.5	18.6 ± 23.1	16.6 ± 19.1	14.5 ± 19.3	<0.001
Total energy intake (kcal/d)	2010 ± 618	2014 ± 614	2002 ± 602	2007 ± 619	2006 ± 610	2015 ± 619	<0.001
Alcohol intake (g/d)	10.1 ± 13.4	11.0 ± 14.4	11.6 ± 15.3	11.9 ± 15.5	12.3 ± 16.6	13.1 ± 17.5	<0.001
Caffeine intake (mg/d)	228 ± 245	235 ± 248	229 ± 241	238 ± 243	244 ± 247	251 ± 254	<0.001
Dietary fiber intake (g/d)	21.8 ± 7.3	21.4 ± 7.0	21.1 ± 6.9	20.8 ± 6.6	20.7 ± 6.7	20.4 ± 6.9	<0.001

[1] NSAIDs, nonsteroidal antiinflammatory drugs; METs, metabolic equivalent tasks, defined as a multiple of metabolic equivalents of sitting at rest.
[2] $\bar{x}$ ± SD (all such values).

TABLE 3

Multivariate-adjusted relative risks (RRs) of symptomatic gallstone disease (GSD) according to height-adjusted waist circumferences among US men who participated in the Health Professionals Follow-Up Study[1]

	Height-adjusted waist circumference (cm)						*P* for trend
	<86.4	86.4 to <90.2	90.2 to <93.7	93.7 to <97.3	97.3 to <102.6	≥102.6	
Cases of GSD (*n*)	97	131	154	179	239	317	—
Person-years	44 956	43 606	43 457	44 107	44 380	43 678	—
RR							
Model 1[2]	1.00	1.29 (0.99, 1.68)	1.42 (1.10, 1.83)	1.56 (1.22, 2.01)	2.01 (1.58, 2.56)	2.66 (2.11, 3.35)	<0.001
Model 2[3]	1.00	1.28 (0.98, 1.67)	1.38 (1.07, 1.79)	1.51 (1.18, 1.95)	1.92 (1.51, 2.44)	2.45 (1.94, 3.11)	<0.001
Model 3[4]	1.00	1.22 (0.93, 1.61)	1.30 (0.98, 1.71)	1.41 (1.07, 1.88)	1.80 (1.35, 2.39)	2.29 (1.69, 3.11)	<0.001

[1] 95% CIs in parentheses.
[2] Age adjusted.
[3] A multivariate model that included adjustment for the following: age (5-y categories), physical activity (quintiles), dietary fiber intake (quintiles), regular use of thiazide diuretics (yes or no), regular use of nonsteroidal antiinflammatory drugs (yes or no), pack-years of smoking (6 categories), alcohol intake (5 categories), caffeine intake (quintiles), and total energy intake (quintiles).
[4] Identical to model 2 except for additional adjustment for BMI in 1986, BMI at 21 y of age, and weight change during the past 2 y.

of 1.07 (95% CI: 1.04, 1.09). The men with a waist-to-hip ratio ≥0.99 had a multivariate relative risk of 1.78 (95% CI: 1.38, 2.28; P for trend < 0.001) compared with those with a waist-to-hip ratio < 0.89. As a continuous variable, each 0.1 increment of waist-to-hip ratio was associated with a relative risk of 1.29 (95% CI: 1.15, 1.44).

In the age-adjusted model, the men with a crude waist circumference ≥102.9 cm (40.5 in) had a relative risk of 2.63 (95% CI: 2.06, 3.35; P for trend < 0.001) compared with those with a crude waist circumference <86.4 cm (34 in) (data not shown). In the multivariate model that adjusted simultaneously for regional and total adiposity measures as well as for other risk factors, the men with a crude waist circumference ≥ 102.9 cm (40.5 in) had a relative risk of 2.14 (95% CI: 1.57, 2.91) compared with those with a crude waist circumference <86.4 cm (34 in) (data not shown). As a continuous variable, each additional 2.54 cm (1 in) of crude waist circumference was associated with a relative risk of 1.06 (95% CI: 1.04, 1.08).

To evaluate the potential for detection bias due to increased medical surveillance of overweight men, we additionally excluded 12 906 men without a routine medical check-up during the first 2-y follow-up period. The multivariate relative risk for the men with a waist-to-hip ratio ≥ 0.99 was 1.53 (95% CI: 1.11, 2.12; P for trend $= 0.009$) compared with those with a waist-to-hip ratio <0.89. The men with a height-adjusted waist circumference ≥102.6 cm (40.4 in) had a relative risk of 2.08 (95% CI: 1.39, 3.10; P for trend < 0.001) compared with those with a height-adjusted waist circumference <86.4 cm (34 in).

We considered the possibility that, because of awareness of the associations between obesity and gallstone disease, physicians may be more likely to diagnose gallstones in asymptomatic fat men. To address this potential bias, we further excluded 517 subjects with unremoved stones, which were presumably less symptomatic, and limited the analysis to subjects who had a cholecystectomy. The multivariate relative risk for the men with a waist-to-hip ratio ≥ 0.99 was 1.71 (95% CI: 1.22, 2.40; P for trend $= 0.009$) compared with those with a waist-to-hip ratio <0.89. The men with a height-adjusted waist circumference ≥102.6 cm (40.4 in) had a relative risk of 2.09 (95% CI: 1.37, 3.17; P for trend $= 0.003$) compared with those with a height-adjusted waist circumference <86.4 cm (34 in).

TABLE 4

Multivariate-adjusted relative risks (RRs) of symptomatic gallstone disease (GSD) according to waist-to-hip ratios among US men who participated in the Health Professionals Follow-Up Study[1]

	Waist-to-hip ratio						*P* for trend
	<0.89	0.89 to <0.92	0.92 to <0.94	0.94 to <0.96	0.96 to <0.99	≥0.99	
Cases of GSD (*n*)	93	158	164	193	224	285	—
Person-years	43 514	52 506	41 158	40 593	40 666	45 747	—
RR							
Model 1[2]	1.00	1.29 (0.99, 1.67)	1.63 (1.26, 2.11)	1.84 (1.43, 2.36)	2.07 (1.62, 2.65)	2.26 (1.78, 2.86)	<0.001
Model 2[3]	1.00	1.28 (0.99, 1.66)	1.59 (1.23, 2.05)	1.76 (1.37, 2.27)	1.96 (1.53, 2.51)	2.09 (1.65, 2.66)	<0.001
Model 3[4]	1.00	1.22 (0.94, 1.58)	1.48 (1.15, 1.92)	1.61 (1.25, 2.07)	1.73 (1.35, 2.23)	1.78 (1.38, 2.28)	<0.001

[1] 95% CIs in parentheses.
[2] Age adjusted.
[3] A multivariate model that included adjustment for the following: age (5-y categories), physical activity (quintiles), dietary fiber intake (quintiles), regular use of thiazide diuretics (yes or no), regular use of nonsteroidal antiinflammatory drugs (yes or no), pack-years of smoking (6 categories), alcohol intake (5 categories), caffeine intake (quintiles), and total energy intake (quintiles).
[4] Identical to model 2 except for additional adjustment for BMI in 1986, BMI at 21 y of age, and weight change during the past 2 y.

TABLE 5

Multivariate-adjusted relative risks (RRs) of symptomatic gallstone disease (GSD) according to BMI in 1986 among US men who participated in the Health Professionals Follow-Up Study[1]

	BMI (kg/m^2)								*P* for trend
	<22.2	22.2 to <23.3	23.3 to <24.1	24.1 to <25.0	25.0 to <25.8	25.8 to <26.7	26.7 to <28.5	≥28.5	
Cases of GSD (*n*)	79	120	125	112	137	141	170	209	—
Person-years	30 634	35 175	30 992	33 019	31 382	33 690	32 212	32 123	—
RR									
Model 1[2]	1.00	1.34 (1.00, 1.79)	1.55 (1.17, 2.06)	1.30 (0.97, 1.73)	1.64 (1.24, 2.16)	1.56 (1.18, 2.05)	1.98 (1.52, 2.60)	2.49 (1.92, 3.23)	<0.001
Model 2[3]	1.00	1.38 (1.03, 1.83)	1.58 (1.19, 2.10)	1.31 (0.98, 1.75)	1.63 (1.24, 2.16)	1.54 (1.16, 2.03)	1.90 (1.45, 2.45)	2.30 (1.76, 3.00)	<0.001
Model 3[4]	1.00	1.24 (0.92, 1.67)	1.32 (0.97, 1.79)	1.03 (0.75, 1.42)	1.21 (0.88, 1.67)	1.07 (0.77, 1.48)	1.22 (0.88, 1.71)	1.29 (0.91, 1.85)	0.18

[1] 95% CIs in parentheses.

[2] Age adjusted.

[3] A multivariate model that included adjustment for the following: age (5-y categories), weight change during the past 2 y (5 categories), physical activity (quintiles), dietary fiber intake (quintiles), regular use of thiazide diuretics (yes or no), regular use of nonsteroidal antiinflammatory drugs (yes or no), pack-years of smoking (6 categories), caffeine intake (quintiles), alcohol intake (5 categories), and total energy intake (quintiles).

[4] Identical to model 2 except for additional adjustment for height-adjusted waist circumference.

We compared the men in the highest BMI category (BMI ≥ 28.5) with those in the lowest BMI category (BMI <22.2) and found that the men in the highest BMI category had an age-adjusted relative risk of 2.49 (95% CI: 1.92, 3.23; *P* for trend < 0.001). The relative risk was slightly attenuated (2.30; 95% CI: 1.76, 3.00; *P* for trend < 0.001) after additional adjustment for potential confounders (**Table 5**). When height-adjusted waist circumference was added to the multivariate model, the relative risks associated with the 8 BMI categories were all markedly attenuated and became nonsignificant. Compared with the men in the lowest BMI category (BMI <22.2), those in the highest BMI category (BMI ≥28.5) had a multivariate relative risk of 1.29 (95% CI: 0.91, 1.85; *P* for trend = 0.18).

DISCUSSION

In this large prospective cohort study, we found that both a higher waist-to-hip ratio and a higher waist circumference were significantly associated with a higher risk of symptomatic gallstone disease in men, even after BMI was controlled for. These variables appeared to capture additional information about risk that was not encompassed by BMI. Control for several potential confounders had only a small effect on these relations. Our results suggest that abdominal obesity and fat distribution may be important for identifying men at high risk of gallstone disease.

In this cohort, consistently high follow-up rates reduced the possibility that our results were biased by men lost to follow-up. It is also unlikely that self-reported anthropometric measurements were influenced by gallstone disease because we collected the data on baseline measurements before the endpoint. In addition, we have shown the validity of self-reported measurements of body weight and waist and hip circumferences (26).

The validity of BMI as a measure of adiposity or body fatness has been assessed by comparison with densitometry. Correlation coefficients with percentage of body fat have generally been between ≈0.6 and ≈0.8 (32). However, BMI as a useful measure of overall obesity does not distinguish between fat and lean body mass and, therefore, may not be a perfect measure of adiposity, particularly in older adults. Adiposity in older persons may increase even though weight or BMI remains stable or even decreases because of the loss of lean body mass due to chronic diseases or inactivity (33, 34). Thus, BMI has limitations as an indication of fatness (27). Fat mass tends to accumulate intraabdominally with age (35), so the importance of abdominal adiposity in metabolic disturbances and health hazards is greater in older people (36). Because a large waist is an unambiguous indicator of excess body fat except in the presence of abdominal tumors or ascites, waist measurement may be a better estimate of overall body fat than is BMI. In this cohort, we previously described age-related patterns of obesity (37). On average, BMI peaks among men at ≈60 y of age and declines thereafter, whereas average waist circumference and waist-to-hip ratio increase through all age groups. Because variation in BMI may reflect varying rates of loss of lean body mass as well as variations in adiposity, BMI may not be an optimal measure of obesity, particularly in men, who have more lean body mass than women do.

The absence of an independent association between BMI and symptomatic gallstone disease, after control for height-adjusted waist circumference, which was a significant predictor, was due to the high correlation between BMI and height-adjusted waist circumference ($r = 0.8$). Because of the large sample size and the sufficient residual variation in the height-adjusted waist circumference variable after control for BMI, we were able to statistically differentiate the effects of height-adjusted waist circumference and BMI. From the biological perspective, BMI becomes primarily a surrogate of lean body mass when BMI and height-adjusted waist circumference are included in the same model, because the variation in BMI attributable to adiposity is essentially controlled by the height-adjusted waist circumference variable. Another plausible explanation is that central fat distribution may be a more important risk factor for gallstone occurrence in men than is overall obesity.

Epidemiologic data concerning the relation between abdominal obesity and gallstone disease are sparse and controversial. Our results are consistent with those of a national, population-based study of 6688 US men in which ultrasonography was used to assess cholelithiasis or evidence of cholecystectomy and that reported a relation between waist-to-hip ratio and gallbladder disease (18). In addition, a population ultrasonographic survey of gallstone prevalence among 838 middle-aged men in the United Kingdom reported that gallstone disease had a stepwise relation with waist-to-hip ratio (20). However, an ultrasonographic survey in a Mexican population reported that waist-to-hip ratio was not related to gallbladder disease (23). In a population study of Japanese middle-aged, male military officials, waist-to-hip ratio tended to be associated positively with prevalent gallstones and history of cholecystectomy (21).

Both waist circumference measures and waist-to-hip ratios are relatively easy to obtain and appear to impart clinically useful information regarding the risk of gallstone disease. A larger waist circumference or waist-to-hip ratio among subjects of equal weight may be a marker of increased abdominal visceral adiposity and of overall adiposity. However, individual circumference measures, rather than waist-to-hip ratios, have less measurement error (27) and may be more practical for weight guidelines. In addition, the magnitude of excess risk for waist circumference measures was slightly stronger than that for waist-to-hip ratios. Thus, waist circumference measures may be a better predictor. Adjusting waist circumference for height did not appreciably influence the magnitude of the association with gallstone risk; because simple waist circumference measurements are easy to perform, they may have practical importance in clinical settings.

Several reviews outlined the metabolic complications of obesity and fat distribution (38–40). There are plausible biological pathways through which abdominal adiposity might cause the development of gallstone disease. In one study, gallbladder volume in the fasting state increased with increasing intraabdominal fat mass and in subjects with impaired glucose tolerance (41). The pathogenesis of gallstones in the obese subjects appeared to be influenced by total body fat mass and its regional distribution, possibly via mutual association with glucose tolerance. Defective gallbladder motility has also been suggested as a pathway, but the evidence is far from conclusive (42). Note that increased free fatty acid influx and insulin resistance may be associated with abdominal obesity. Visceral fat is more metabolically active than is nonvisceral fat and thus increases hepatic exposure to free fatty acids and decreases insulin sensitivity. Studies have suggested a relation between gallstone disease and the metabolic syndrome linked to abdominal obesity, of which the cardinal feature is hyperinsulinemia. Hyperinsulinemia may cause increased hepatic cholesterol secretion and cholesterol supersaturation by activating hydroxymethylglutaryl coenzyme A reductase or by upregulating hepatocyte LDL receptors (43, 44). Insulin might also increase gallstone risk through an effect on gallbladder motility (45). A positive association between hyperinsulinemia and gallbladder disease has been shown (46).

Although our study had several strengths, there were limitations. The outcomes were restricted to men with cholecystectomy or diagnostically confirmed but unremoved symptomatic gallstones. Asymptomatic gallstones were not included because most would have been detected incidentally. We did not attempt to estimate the incidence of gallstone formation but rather the incidence of newly symptomatic gallstones. Thus, the analyses focused on clinically relevant gallstone disease. An additional limitation was that abdominal circumference and waist-to-hip ratio were measured at baseline, but potential changes in abdominal girth over the follow-up periods were not measured.

It is possible that abdominal obesity may increase the risk of other medical morbidities and that the men in the present study may have been more likely than the typical US man to see a physician for medical care throughout the follow-up periods and to have gallstones diagnosed. We addressed the possibility of detection bias by excluding men without a routine medical check-up during the first 2-y follow-up period and by limiting the analysis to subjects who had a cholecystectomy (ie, excluding subjects with unremoved stones), which were presumably less symptomatic and more prone to detection bias. After these exclusions, the positive associations persisted and were still significant.

It was not possible to perform systematic screening in this study population. Some undiagnosed gallstone cases may have been present at baseline before the reporting of anthropometric measurements. However, the presence of asymptomatic gallstones at baseline is unlikely to have been associated with the reporting. Because relative risk estimation in follow-up studies would not be biased by uniform underascertainment (29), our results were probably not biased because of asymptomatic gallstones.

In conclusion, these prospective data suggest the presence of a significant association between abdominal adiposity and the incidence of symptomatic gallstone disease. As measures of abdominal adiposity, abdominal circumference and waist-to-hip ratio predicted the risk of gallstones independently of BMI.

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REFERENCES

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999;117:632–9.
2. National Hospital Discharge Survey: 2000 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 2003:153.
3. Cohen DE. Pathogenesis of gallstones. In: Zakim D, Boyer TD, eds. Hepatology: a textbook of liver disease. 4th ed. Philadelphia: WB Saunders, 2002:1713–43.
4. Diehl AK, Schwesinger WH, Holleman DR Jr, Chapman JB, Kurtin WE. Gallstone characteristics in Mexican Americans and non-Hispanic whites. Dig Dis Sci 1994;39:2223–8.
5. Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med 1993;119:1029–35.
6. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr 1992;55:652–8.
7. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med 1989;321:563–9.
8. Maurer KR, Everhart JE, Knowler WC, Shawker TH, Roth HP. Risk factors for gallstone disease in the Hispanic populations of the United States. Am J Epidemiol 1990;131:836–44.
9. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Hepatology 1997;26:809–18.
10. Barbara L, Sama C, Morselli Labate AM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. Hepatology 1987; 7:913–7.
11. Kono S, Kochi S, Ohyama S, Wakisaka A. Gallstones, serum lipids, and glucose tolerance among male officials of self-defense forces in Japan. Dig Dis Sci 1988;33:839–44.
12. Scragg RKR, McMichael AJ, Baghurst PA. Diet, alcohol and relative weight in gallstone disease: a case-control study. Br Med J (Clin Res Ed) 1984;288:1113–9.
13. Michels KB, Greenland S, Rosner BA. Does body mass index adequately capture the relation of body composition and body size to health outcomes? Am J Epidemiol 1998;147:167–72.
14. Carey V, Walters E, Colditz G, et al. Body fat distribution and risk of non-insulin-dependent diabetes in women. Am J Epidemiol 1997;145: 614–9.

15. Despres JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497–511.
16. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982;54:254–60.
17. Dubrac S, Parquet M, Blouquit Y, et al. Insulin injections enhance cholesterol gallstone incidence by changing the biliary cholesterol saturation index and apo A-I concentration in hamsters fed a lithogenic diet. J Hepatol 2001;35:550–7.
18. Ruhl CE, Everhart JE. Relationship of serum leptin concentration and other measures of adiposity with gallbladder disease. Hepatology 2001; 34:877–83.
19. Haffner SM, Diehl AK, Stern MP, Hazuda HP. Central adiposity and gallbladder disease in Mexican Americans. Am J Epidemiol 1989;129: 587–95.
20. Heaton KW, Braddon FEM, Emmett PM, et al. Why do men get gallstones? Roles of abdominal fat and hyperinsulinemia. Eur J Gastroenterol Hepatol 1991;3:745–51.
21. Everhart JE, Yeh F, Lee ET, et al. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. Hepatology 2002;35:1507–12.
22. Kodama H, Kono S, Todoroki I, et al. Gallstone disease risk in relation to body mass index and waist-to-hip ratio in Japanese men. Int J Obes Relat Metab Disord 1999;23:211–6.
23. Kono S, Shinchi K, Todoroki I, et al. Gallstone disease among Japanese men in relation to obesity, glucose intolerance, exercise, alcohol use, and smoking. Scand J Gastroenterol 1995;30:372–6.
24. Gonzalez Villalpando C, Rivera Martinez D, Arredondo Perez B, et al. High prevalence of cholelithiasis in a low income Mexican population: an ultrasonographic survey. Arch Med Res 1997;28:543–7.
25. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC. Effectiveness of various mailing strategies among non-respondents in a prospective cohort study. Am J Epidemiol 1990;131:1068–71.
26. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
27. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press, 1998.
28. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
29. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.
30. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med 1988;7:205–22.
31. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9: 1501–15.
32. Rosner B, Hennekens CH, Kass EH, Miall WE. Age-specific correlations analysis of longitudinal blood pressure data. Am J Epidemiol 1977; 106:306–13.
33. Fischer J, Johnson MA. Low body weight and weight loss in the aged. J Am Diet Assoc 1990;90:1697–706.
34. Forbes GB, Reina JC. Adult lean body mass declines with age: some longitudinal observations. Metabolism 1970;19:653–63.
35. Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F. Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. Am J Clin Nutr 1986;44: 739–46.
36. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. J Clin Invest 1983;72:1150–62.
37. Giovannucci E, Rimm EB, Chute CG, et al. Obesity and benign prostate hyperplasia. Am J Epidemiol 1994;140:989–1002.
38. Despres JP. Health consequences of visceral obesity. Ann Med 2001; 33:534–41.
39. Grundy SM. Metabolic complications of obesity. Endocrine 2000;13: 155–65.
40. Bouchard C, Despres JP, Mauriege P. Genetic and nongenetic determinants of regional fat distribution. Endocr Rev 1993;14:72–93.
41. Hendel HW, Hojgaard L, Andersen T, et al. Fasting gall bladder volume and lithogenicity in relation to glucose tolerance, total and intra-abdominal fat masses in obese non-diabetic subjects. Int J Obes Relat Metab Disord 1998;22:294–302.
42. Petroni ML. Gallbladder motor function in obesity. Aliment Pharmacol Ther 2000;14(suppl):48–50.
43. Nepokroeff CM, Lakshmanan MR, Ness GC, Dugan RE, Porter JW. Regulation of the diurnal rhythm of rat liver beta-hydroxy-beta-methylglutaryl coenzyme A reductase activity by insulin, glucagon, cyclic AMP and hydrocortisone. Arch Biochem Biophys 1974;160:387–96.
44. Chait A, Bierman EL, Albers JJ. Low-density lipoprotein receptor activity in cultured human skin fibroblasts. Mechanism of insulin-induced stimulation. J Clin Invest 1979;64:1309–19.
45. Gielkens HAJ, Lam WF, Coenraad M, et al. Effect of insulin on basal and cholecystokinin-stimulated gallbladder motility in humans. J Hepatol 1998;28:595–602.
46. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000;31:299–303.